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09/606,909	06/29/2000	Ronald J. Pettis	P-4901	7814

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EXAMINER	
HAYES, MICHAEL J	
ART UNIT	PAPER NUMBER
3734	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/606,909	PETTIS ET AL.	
	Examiner	Art Unit	
	Michael J. Hayes	3734	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7,10-24,29 and 32-39* is/are pending in the application.

4a) Of the above claim(s) *17-24 and 32-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7,10-16 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 June 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Newly submitted claims 32-39 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the newly submitted species are directed to methods of treatment of toxicity, controlling thrombosis, and controlling infection; and the use of various drugs such as antitoxin, pain controllers, opioids, analgesics, anesthetics, heparin, coumadin, warfarin, and antibiotics. Prosecution has been developed concerning the species method of delivering a hormone, such as PTH or insulin into a patient's intradermal layer. Since the new claims 32-39 are directed to different species than the claims under prosecution, the new claims are withdrawn. Claim 29 is considered generic and if allowed in generic form the additional species recited in new claims 32-39 will be considered on the merits.

Applicant argues that prosecution has not been limited to hormones such as PTH and insulin. The examiner maintains the restriction because, while newly proposed claims 32-39 are species to the elected generic invention recited in claim 29, these newly proposed claims are directed to other species than that currently examined. Species directed to PTH and insulin were constructively elected and examined in claim 7. The addition of newly proposed claims 32-39 of methods of administration of more drug species are held to be drawn to further species.

Since applicant has received an action on the merits for the previously presented species, this species has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 32-39 are withdrawn from consideration as being directed to a non-elected species. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 2-7, 10-24, 29, and 32-39 are pending. Claims 17-24 and 32-39 are withdrawn.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

Claim 14 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The outlet exposed height of 0 - 1mm, as recited in dependent claim 14 is recited in the independent claim 29.

Claim Rejections - 35 USC § 112

New Matter Rejection Withdrawn

The new matter rejection of claims 2-5, 10-16, and 29 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn. The examiner agrees that the specification, as originally filed, describes a method of administering a drug to a human applying pressure to effectively control the rate of delivery so that the drug is delivered into the intradermal (ID) compartment to exhibit a pharmacokinetic profile similar to subcutaneous (SC) delivery, but with higher maximum plasma concentration (Cmax) and a higher bioavailability. The description of this higher Cmax and higher bioavailability is found in Applicants' disclosure of a difference between ID and SC delivery (specification, pg. 6, ll. 2-4; pg 7, ll. 22-23). Here Applicants state "ID infusion or injection often provides higher plasma levels of drug

than conventional SC administration, particularly for drugs which are susceptible to *in vivo* degradation or clearance" and that ID infusion may provide higher plasma levels for some drugs. Applicant continues that these higher plasma levels would then "allow for smaller doses of the substance to be administered . . . ." (specification, pg. 6, ll. 4-5). The presence of higher plasma levels of drug and the resultant use of smaller doses would be recognized by one of ordinary skill in the art as showing a higher bioavailability and Cmax pharmacokinetic profile.

35 U.S.C. 112(1) Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of enablement

Claims 2-5, 10-16, and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivering **insulin and PTH** to an intradermal layer, does **not reasonably provide enablement** for ID delivery of **all drugs** to achieve higher maximum plasma concentration and higher bioavailability than that achieved with SC delivery. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicant's disclosure does not support a claim dominating every drug and its ID delivery to a human subject to achieve a pharmacokinetic profile similar to SC delivery, but with a higher Cmax and

bioavailability. There is a lack of reasonable correlation between the disclosure and the broad scope of protection of the claims for ID delivery of every drug.

Applicant's submitted declaration by Dr. Ronald J. Pettis (2nd Pettis Declaration, received 10/7/05) describes two examples where the ID and SC deliveries did not result in increased Cmax and bioavailability (see Para. 6-11). These paragraphs stand in contrast to paragraphs 12-16 of submitted declaration by Dr. Gerald B. Kasting (received 10/7/05). In the Kasting declaration, Dr. Kasting states that a scientist, following the ID delivery teachings of the Pettis method disclosed in the present application, would be able to obtain "a pharmacokinetic profile with a higher Cmax and AUC as compared to delivery of the same drug to the subcutaneous compartment." (Para. 13); and a "scientist would simply assay a series of pressures to arrive at the optimal pressure to achieve the desired pharmacokinetic profile for the drug of his choice." (Para. 12) Clearly the failure of Dr. Pettis to achieve an increased Cmax and bioavailability with Genotropin™ and Almotripan, as described in his declaration, shows the unpredictable nature of the recited delivery method. Dr. Pettis has not provided any data that shows higher Cmax and bioavailability with these drugs.

The experimentation required to perform the claimed method is considered undue because of the breadth of the claims, low level of predictability in the art, lack of direction provided by the disclosure, scarcity of working examples, and quantity of experimentation required to use the claimed method. In consideration of these factors the claims are rejected because the recited scope is not enabled.

Applicants claim a method of ID delivery of all drugs to achieve a pharmacokinetic profile similar to SC delivery, but with a higher Cmax and

bioavailability. Applicants have claimed a drug delivery method encompassing all drugs. While claiming a method for all drugs, Applicants have only described two examples. These two examples describe ID delivery of insulin and human parathyroid hormone 1-34 (PTH). There is no discussion of extrapolation of these examples to other drugs.

Further evidence that the additional experimentation needed to carry out the claimed method is undue is found in the art recognized variability of pharmacokinetics in patients. Pharmacokinetic profiles are dependant upon the rate of drug absorption, drug metabolism, and drug elimination in a patient (See The Merck Manual of Diagnosis and Therapy, 1999, 17th Ed., Beers & Berkow, ed., Merck Research Laboratories, Division of Merck & Co., Inc., Whitehouse Station, NJ, pp. 2566-2571). A patient's age, physical health, disease state, stress level, use of other drugs, and tissue oxygen concentration vary a drug's pharmacokinetics in ways that are not fully understood (See discussion of *Variability in Parameter Values* in The Merck Manual of Diagnosis and Therapy, pp. 2570-2571). The discussion here states that some age and weight effects on pharmacokinetics are established, but "exceptions are common," that Hepatic dysfunction changes metabolic clearance with no good predictors of the changes, and that many diseases, as well as interactions with other drugs, alter pharmacokinetics. Additional factors include changes in dose, dosing rate, or therapy duration. The unpredictable variability of pharmacokinetics and the large number of factors influencing pharmacokinetics is also addressed in the following publications:

Pharmacokinetics and Pharmacodynamics in the critically ill patient, G.R. Park, Xenobiotica, 1993, Vol. 23, No. 11, 1195-1230. This publication discusses the variability encountered in the critically ill patient due to the many factors affecting drug

elimination. These factors include age, stress, diet, other drugs administered, disease state and level of organ function as well as method of support of failing organs (See fig. 2; pgs. 1197-1211).

Influence of Injection Site and Route on Medication Absorption, Erstad, B.L. et. al., Hospital Pharmacy, Vol. 28, No. 9, 853-854, 872-873. This publication discusses the affect of drug formulation, site of injection, and particular blood flow to an area as affecting pharmacokinetics after ID injections. Aging, malnutrition, disease state, tissue composition, and exercise are listed as affecting drug absorption and therefore its pharmacokinetics (See pgs. 853-854; 872-873).

A large number of experiments would be required to find the correct parameters to achieve the claimed method in each patient on whom the claimed method was used. At most the specification merely invites one of ordinary skill in the art to experiment with various drugs to see if a particular drug will show increased Cmax and bioavailability in a particular patient.

Applicant's statement that experiments using various pressures combined with blood tests over a period of time (Applicant's data show approximately 6 hrs of experimentation per pressure value would be expected) along with various delivery sites on a patient's skin and repeating the same conditions except with subcutaneous injection would be required for each drug desired to be used in the claimed method. This would require an inordinate number of experiments. Applicant provides guidance for one example with insulin and one example with PTH. This brief disclosure is insufficient to support a method of delivering all drugs, for all patients.

35 U.S.C. 112(2) Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-7, 10-16, and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 recites that the pharmacokinetic profile between ID and SC injections is greater with respect to bioavailability and Cmax, but the pharmacokinetic profile between ID and SC injections is also similar. The claims recite the presence of differences and similarities between the two injection methods, but it is not clear what similarities Applicant is reciting in the claims. There is no clear description in the specification of what the claimed similarities of ID and SC injections would entail. This lack of description blurs the metes and bounds of the claims because it is not known what similarities Applicant is reciting in the claims.

In the specification, pg. 3, ll. 9-15 Applicant discusses how the ID method shows "very similar" pharmacokinetics with SC delivery, but with the difference of "reduction or elimination of pain for the patient." Additionally, Applicant makes other statements that the ID method is considered the same as SC delivery, (See original specification: pg. 3, line 35 - pg. 4, line 1; pg. 7, ll. 11-12; and pg. 8, ll. 13-15) except for resulting pain. However, there is no description to clarify what recited pharmacokinetic aspects are similar between the ID and SC delivery methods while at the same time showing a higher Cmax and higher bioavailability.

In the working examples with insulin Applicant states that ID and SC show "similar plasma insulin levels and onset periods." (pg. 7, ll. 11-12). How the plasma levels are similar, but also with different Cmax is not particularly pointed out nor distinctly claimed.

The statistical error shown in figs. 1 and 4 are inconclusive concerning the values of Cmax for ID and SC delivery. Also the bioavailability cannot be determined from the data shown in the figures because the Cmax is inconclusive and the area under the curve (AUC) is not represented as they would need to be shown to be conclusive for bioavailability measurements (i.e., data values do not show the complete elimination of the drug as is required for an accurate bioavailability determination). The data in these figures do not assist in determining the similarities or differences between the ID and SC delivery methods.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-7, 10-16, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over GROSS (US Patent No. 5,848,991) or GROSS (US Patent No. 5,807,375) in view of PRAUSNITZ (US Patent No. 6,611,707), AUTRET, PURI (*An investigation of the intradermal route as an effective means of immunization for microparticulate vaccine delivery systems*), D'Antonio et al. (US Patent No. 6,056,716),

SRIVASTAVA (US Patent No. 6,007,821), and The Merck Manual of Diagnosis and Therapy (17th ed.) (1999).

Gross '991 discloses a method of delivering various drugs, particularly insulin and hormones, intradermally (3:40-41; 6:56 - 7:20) using a single needle having a length from the housing of 300μm - 3mm (4:10-35). This length would put the needle outlet at a depth within the range of about 250 μm - 2mm or 750μm - 1.5mm when the housing is set against a patient's skin to achieve ID delivery. Additionally, this depth would be required to meet the disclosure of Gross'991 to deliver the drugs intradermally, as this is the depth of the intradermal layer. Gross '375 discloses a method of drug delivery using a needle that extends into the intradermal layer to deliver insulin into this intradermal layer (col. 5, line 25 - col. 6, line 34; col. 10, ll. 24-30, col. 14, ll. 40-62). The needle length is chosen from the range 300μm - 3mm that extends from the housing to deliver into the intradermal layer at a depth of about 250 μm - 2mm or 750μm - 1.5mm which is the depth of the intradermal layer (col. 10, ll. 23-27).

Gross '991 and Gross '375 are silent with respect to the needle outlet exposed height of 0 - 1mm and the pharmacokinetic profile of the ID delivered drugs. Prausnitz teaches the use of needles with zero exposed height to deliver drugs into the skin. (col. 3, ll. 27-38). It would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Prausnitz in the method of Gross '991 or Gross '375 in order to provide a known flow dynamic as desired from the end of the delivery needle. The zero exposed height needle as disclosed in Prausnitz would be known to provide a substantially longitudinally directed flow as opposed to a radially directed flow component as found in beveled needles when liquid exits the needle opening. One of

ordinary skill in the art would know to select a particular exposed height needle dependent upon the desired flow delivery.

Autret, Puri, D'Antonio, and Srivastava each suggest a greater Cmax and bioavailability in intradermal injections as compared to subcutaneous injections (see Autret fig. 1; Puri, pgs. 2609-2610; D'Antonio col. 29, lines 3-23; and Srivastava col. 19, line 60 - col. 20, line 25). Autret discloses intradermal injection of a hormone resulting in a pharmacokinetic profile similar to subcutaneous delivery, but with a higher plasma level and bioavailability as assessed by Cmax and Tmax (fig. 1). The Merck Manual is referenced here as evidence showing the various methods that bioavailability is assessed (see pg. 2560). Puri discloses that lower doses can be used with ID delivery than with SC delivery (pg. 2610). The ability to use lower doses is the practical result when a higher Cmax and bioavailability is achieved with equal dosages; whereby the required Cmax and bioavailability is still achieved to treat the illness. As drug treatment efficacy depends on Cmax and bioavailability, one of ordinary skill in the art would recognize that when equal ID and SC dosages give higher Cmax and bioavailability via the ID route, then the ID dosage can be reduced to treat a patient. D'Antonio discusses experimental evidence in the prior art that indicate ID injections into the dermis are many times more powerful than SC injections. This allows greatly reduced dosages to be used (col. 29, ll. 3-9). The ability to use lower dosages show that a higher Cmax and bioavailability is achieved with ID over SC delivery. Srivastava describes a method of ID delivery of drug treatments where the ID injections typically required lower dosages than SC delivery (col. 20, ll. 3-7).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Autret, Puri, D'Antonio, or Srivastava in the drug delivery method of Gross '991 and Prausnitz or Gross '375 and Prausnitz to deliver effective drug treatments at particular pressures and flow rates to achieve higher Cmax and bioavailability with intradermal injection as compared to subcutaneous injection in order to effectively treat patients using lower dosages, thereby saving drug costs and inventories. Conserving drug inventories and lowering the costs of drug treatments is desirable in the drug delivery field to maximize the treatment availability of the drug, and is something one of ordinary skill in the art is constantly looking to achieve.

Re claim 4 Gross '991 or Gross '375 does not disclose using multiple needles. Prausnitz teaches using multiple needles to achieve the desired drug injection flow (col. 3, line 27 - col. 4, line 7). It would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Prausnitz in the method of Gross '991 or Gross '375 in order to achieve a larger drug delivery area and treatment zone.

Re claim 16 Gross '991 or Gross '375 does not disclose flow control by needle spacing or diameter. Prausnitz teaches using flow control by varying needle diameter or spacing (col. 4, ll. 3-7; col. 8, ll. 54-67). It would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Prausnitz in the method of Gross '991 or Gross '375 in order to control flow parameters to vary injection rates and effects as desired.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2-7, 10-16, 29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 10 of copending Application No. 10/868482; claims 1, 2, 7, 8, 50 of copending Application No. 10/867908; claims 1-7, 9, 13, 16, 26, 28-30, 32, 35-41, 46-48, 50, 52-54, 57, 59, and 62-64 of copending Application No. 10/487485; claim 25 of copending Application No. 11/004780; claim 25 of copending Application No. 11/004778; claims 1-3, 8, 10-16 of copending Application No. 10/841992; claims 66 and 76 of copending Application No. 10/803735; claims 22-26, 29-31, 33 of copending Application No. 10/650039; claim 33 of copending Application No. 10/429973; claims 65, 71, 72, 75-77, 82 of copending Application No. 09/893746; claims 31, 32, 36, 37, 39, 49, 67, 73 of copending

Application No. 10/028988; and claims 69, 72, 83-86, 88, 90, 100, 103 of copending Application No. 10/028989 in view of Gross '991 or Gross '375, and Prausnitz, Autret, Puri, D'Antonio, and Srivastava.

Claim 29 recites a method of drug administration by delivering a drug through a hollow needle into the intradermal compartment using a needle with its outlet depth and exposed height in the intradermal compartment and the needle having an exposed height of 0-1 mm so the delivered drug exhibits a pharmacokinetic profile similar to subcutaneous delivery but with a higher maximum plasma concentration and a higher bioavailability. Claims 8 and 10 of 10/868482 recite a method of administering a therapeutic agent into the intradermal compartment to achieve higher bioavailability as compared to another delivery route. These claims do not recite the use of a needle with an exposed height of 0-1 mm to deliver a drug intradermally to achieve higher Cmax along with higher bioavailability over delivering a drug subcutaneously. Gross '991 (3:40-41; 6:56 - 7:20) and Gross '375 teach a method of delivering insulin and hormones intradermally using a needle in a controlled manner (Gross '991; 4:10-35). Prausnitz teaches injecting a drug through multiple needles with a zero exposed height (col. 3, line 27 - col. 4, line 7). Autret, Puri, D'Antonio, and Srivastava each disclose achieving a greater Cmax and bioavailability via intradermal injections as compared to subcutaneous injections (see Autret fig. 1; Puri, pgs. 2609-2610; D'Antonio col. 29, lines 3-9; and Srivastava col. 19, line 60 - col. 20, line 25 as discussed above). It would have been obvious to one of ordinary skill in the art at the time of the invention to use the teachings of Autret, Puri, D'Antonio, Srivastava, Gross '991, Gross '375, and Prausnitz in the claimed method of claims 8 and 10 of Application Nos. 10/868482, in order to provide a

known flow dynamic as desired from the end of delivery needles as a longitudinally directed flow and to effectively treat patients with lower drug costs resulting from using less drugs dosages and maintaining greater drug inventories.

The claims of the other applications listed above: claims 1, 2, 7, 8, 50 of copending Application No. 10/867908; claims 1-7, 9, 13, 16, 26, 28-30, 32, 35-41, 46-48, 50, 52-54, 57, 59, and 62-64 of copending Application No. 10/487485; claim 25 of copending Application No. 11/004780; claim 25 of copending Application No. 11/004778; claims 1-3, 8, 10-16 of copending Application No. 10/841992; claims 66 and 76 of copending Application No. 10/803735; claims 22-26, 29-31, 33 of copending Application No. 10/650039; claim 33 of copending Application No. 10/429973; claims 65, 71, 72, 75-77, 82 of copending Application No. 09/893746; claims 31, 32, 36, 37, 39, 49, 67, 73 of copending Application No. 10/028988; and claims 69, 72, 83-86, 88, 90, 100, 103 of copending Application No. 10/028989 recite similar methods as claims 8 and 10 of application 10/868482. All these claims are directed to delivery of drugs to the intradermal compartment to achieve greater absorption, Cmax, and/or bioavailability. All these claims in view of Gross '991 or Gross '375, and Prausnitz, Autret, Puri, D'Antonio, and Srivastava render claims 29, 2-7, and 10-16 obvious with similar reasoning as stated above with respect to Application 10/868482.

These are provisional obviousness-type double patenting rejections.

Response to Declarations and Arguments

Some of Applicant's arguments do not apply because of the new rejections as discussed above. As some issues remain and are pertinent to Applicant's arguments

submitted 8/23/06 they are addressed below.

Applicant argues that the prior art does not disclose delivery to the ID layer. The examiner disagrees and refers applicant to Gross '991 where the drug delivery is described "to the interior of the dermis" (col. 3, ll. 38-40). Additionally Gross '375 discloses intradermal delivery depending on the condition treated (col. 6, ll. 25-34) and that the needle tip is placed intradermally to accomplish the drug delivery (col. 5, ll. 25-29). Delivery to the intradermal layer is taken as directly stated - that the delivery results in delivering the drug into the ID layer, not outside of this layer, and requires the needle outlet to be within the intradermal layer.

Applicant states that Autret does not recognize higher maximum plasma concentration and bioavailability. The examiner disagrees because the data presented by Autret shows a higher Cmax and a higher bioavailability as assessed by Cmax and Tmax (See fig. 1). The difference in Autret's recognition and Applicant's of their own data appears to be based on differing statistical analysis; however Applicant has not claimed any results with respect to a particular statistical significance. Applicant states that Autret does not recognize any difference between ID and SC deliveries. The examiner notes that in view of the document as a whole, Autret's statements concerning no difference are directed to no "significant" differences and that the figures clearly show a difference. The statistical analysis applied to the experimental data appears to determine what is a significant difference and Applicant has not claimed the difference between ID and SC to be different with respect to a particular statistical analysis.

Applicant's arguments regarding the prior art not showing both higher Cmax and higher AUC are not convincing because Applicant is arguing limitations that are not

recited in the claims or are not the same scope of the claims. The claims recite an ID delivery method giving higher maximum plasma concentration and higher bioavailability, not AUC. The Merck Manual (cited above) states that there are several methods to assess bioavailability, particularly Cmax, Tmax, and AUC. Although AUC may be the most prevalent method to determine bioavailability it is not the sole method. Applicant's specification has not explicitly defined that bioavailability is calculated only by AUC in his invention. Using Cmax and Tmax Autret is seen to show higher bioavailability with ID delivery than SC delivery.

The role of pressure is not consistent in Applicant's arguments. Pressure is acknowledged as a critical feature in the first paragraph on pg. 7 of remarks received 1/06/05, but then Applicant states "Nor is the absolute value at which pressure is applied critical to the claimed invention." (3rd paragraph of remarks received 1/06/05). Since pressure values determine the flow rate one would view it as a critical feature of the claimed method. Applicant's remarks submitted 10/7/05 address the critical and non-critical nature of pressure in his method, but these remarks do not further clarify the issue. Applicant's remarks that application of the correct amount of pressure is critical, but the absolute value of the pressure used is not critical are inconsistent. The absolute value of pressure used is the amount of pressure applied to deliver the drug at a desired rate, and since the value is the amount applied, either both are critical or both are not critical. Furthermore, Applicant's disclosure does not provide any guidance at which pressures are required to achieve the claimed method. Applicant merely invites the skilled artisan to experiment to determine pressure on their own.

Applicant arguments that Puri and D'Antonio are concerned with vaccines, not drugs are not convincing. Applicant has not explicitly defined drugs in the specification to exclude vaccines. Additionally, vaccines such as cancer vaccines are both drugs for treatment (therapeutic vaccines) as well as vaccines to prevent development of cancer (prophylactic vaccine).

Applicant argues that D'Antonio is not concerned with injection of drugs or ID delivery, but focuses on intramuscular injections. This position is not convincing because although D'Antonio discusses intramuscular injections, the benefits of ID delivery over that of intramuscular and subcutaneous delivery is clearly stated at 29:3-9. D'Antonio also states that his invention concerns hypodermic fluid injections for medical treatment for a patient 1:15-17, 22:11-20 (i.e., drug administration). D'Antonio and Puri are cited to show the prior art recognition that delivery to the ID compartment gives a greater Cmax than SC delivery as suggested in the results that a lower dose of drug can be used with ID delivery as compared to SC delivery.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Hayes at (571) 272-4959. The examiner can usually be reached Monday -Thursday, 7:00-4:30, and on alternate Fridays. The fax number for submitting official papers is (571) 273-8300.

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21 December 2006

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